ACS Medicinal Chemistry Letters

In This Issue

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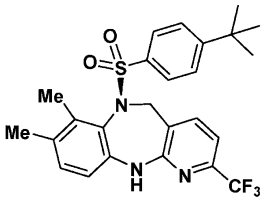
TARGETING THE OBESITY RECEPTOR

The prevalence of obesity is on the rise and is reaching global epidemic proportions. Obesity is a risk factor for morbidity and mortality as it can lead to the development of type 2 diabetes, hypertension, cancer, osteoarthritis, and cardiovascular diseases. While a change of lifestyle is ideal, the current magnitude of the obesity problem demands a search for new antiobesity drugs. Although one drug has been approved for treatment, its efficacy is limited. Thus, the search for new therapeutics with high efficiency and tolerability is still ongoing.

The bombesin receptor plays a role in regulating energy, and its inhibition could lead to obesity. On the other hand, receptor agonists could lead to food intake reduction. Now, Liu et al. (DOI: 10.1021/ml200207w) describe the discovery of bombesin receptor subtype-3 agonists. The group optimized a lead compound obtained from a high-throughput screen, which gave way to novel receptor agonists with high potency and pharmacokinetic properties. One analogue resulted in weight loss in obese mice, showing promise as a potential lead antiobesity therapeutic.



8a

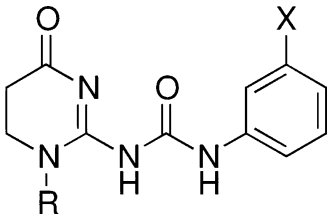
hBRS-3 IC_{50} = 1.4 nM

hBRS-3 EC_{50} = 97 nM (96%Act)

TWEAKING THE OLD ANTAGONIST

It has been shown that metabotropic glutamate receptors play a crucial role in cognitive learning and memory. One subtype, metabotropic glutamate receptor 5, is highly expressed in the brain and has been proposed as an important target for central nervous system disorders such as fragile X syndrome, drug abuse, pain, and anxiety. The imidazole derivative compound fenobam was found to be a potent, negative allosteric modulator of this receptor but has not been approved for treatment due to concern about possible adverse effects.

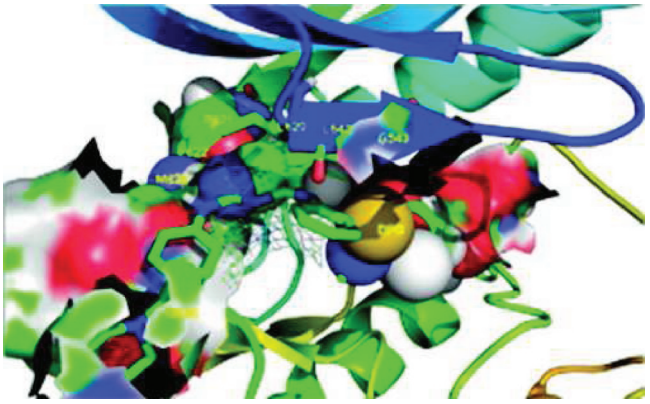
In this issue, Gichinga et al. (DOI: 10.1021/ml200162f) explore the synthesis of a class of compounds that contain similar key moieties in fenobam but have never been tested for their activity as metabotropic glutamate receptor 5 antagonists. Three out of 15 new fenobam analogues were found to be effective metabotropic glutamate receptor 5 antagonists at low concentrations. One compound had efficacy similar to that of fenobam. These compounds represent new leads to pursue for treatment of central nervous system disorders.



SEARCHING FOR AXL KINASE INHIBITORS

AXL is one of three TAM receptor kinases that play pivotal roles in innate immunity. Recent studies point to the role of AXL in oncogenic mechanisms due to its overexpression in a spectrum of human cancers. As an example, suppression of AXL gene expression resulted in decreased pancreatic cell growth. Hence, AXL kinase is becoming an emerging oncology target.

Here, Mollard et al. (DOI: 10.1021/ml200198x) describe their approach in designing AXL kinase inhibitors based on a homology model of the enzyme active site and three related proteins as templates. The authors were able to synthesize potent pyrimidine-based inhibitors of AXL with strong activity against pancreatic cell lines. While highly active, these compounds were also able to bind to other kinases. Further synthetic efforts on these compounds might afford inhibitors with greater specificity in targeting AXL kinase alone while maintaining their potency.



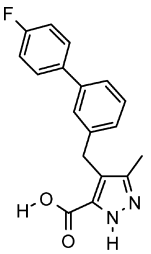
INHIBITORS OF NEW HYPERTENSION TARGET

While the etiology of human hypertension remains largely unknown, hypertension and related cardiovascular diseases persist as one of the leading causes of death worldwide. Despite the availability of various antihypertensive drugs, therapeutics for this rampant disease are still insufficient due to lack of efficacy or associated side effects with current therapy.

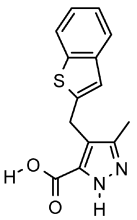
Published: December 8, 2011

dx.doi.org/10.1021/ml200262n | *ACS Med. Chem. Lett.* 2011, 2, 875–876

In this issue, Barawkar et al. (DOI: 10.1021/ml2001938) establish a novel antihypertensive target. L-2-Hydroxy acid oxidase has been pinpointed as a candidate gene for systolic blood pressure quantitative trait locus in rats and has also been linked to hypertension in human. The authors identified this enzyme as a potential target for pharmacological intervention using inhibitors of rat L-2-hydroxy acid oxidase. Compound optimization and evaluation using an established rat model of hypertension yielded efficacious inhibitors of L-2-hydroxy acid oxidase and further support its role in blood pressure regulation.



3



4